

UPDATED AASM RLS GUIDELINES: OUT WITH THE OLD AND IN WITH THE NEW

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Disclosures

Noctrix Health

- Research
- Speaker
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Prevalence of RLS

- 11.1% with any RLS symptoms
- 9.6% with once weekly symptoms
- 3.9-5.6% with twice weekly symptoms
- 2.4-3.4% with RLS symptoms ≥ 2 x/week and negative impact on QOL

SPECIAL ARTICLES

**Treatment of restless legs syndrome and periodic limb movement disorder:
an American Academy of Sleep Medicine clinical practice guideline**

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UPDATED RLS MANAGEMENT ALGORITHM



MAYO CLINIC PROCEEDINGS

CLINICAL PRACTICE
GUIDELINES

An Updated Algorithm for the Management of Restless Legs Syndrome



Michael H. Silber, MBChB; J. Andrew Berkowski, MD; Mark J. Buchfuhrer, MD;
Lourdes M. DelRosso, MD, PhD; Christopher J. Earley, MBBCh, PhD;
Melissa C. Lipford, MD; Mauro Manconi, MD; John W. Winkelman, MD, PhD;
and Rochelle S. Zak, MD; for the Scientific and Medical Advisory Board of the
Restless Legs Syndrome Foundation

So, WHAT CHANGED?

AASM Clinical Guidelines

12. In adults with RLS, the AASM **suggests against the standard use of pramipexole** (conditional recommendation, moderate certainty of evidence). Remarks: pramipexole may be used to treat RLS in patients who place a higher value on the reduction of restless legs symptoms with short-term use and a lower value on adverse effects with long-term use (particularly augmentation).

13. In adults with RLS, the AASM **suggests against the standard use of transdermal rotigotine** (conditional recommendation, low certainty of evidence). Remarks: transdermal rotigotine may be used to treat RLS in patients who place a higher value on the reduction of restless legs symptoms with short-term use and a lower value on adverse effects with long-term use (particularly augmentation).

14. In adults with RLS, the AASM **suggests against the standard use of ropinirole** (conditional recommendation, moderate certainty of evidence). Remarks: ropinirole may be used to treat RLS in patients who place a higher value on the reduction of restless legs symptoms with short-term use and a lower value on adverse effects with long-term use (particularly augmentation).

17. In adults with RLS, the AASM **suggests against the use of clonazepam** (conditional recommendation, very low certainty of evidence).

WHAT CHANGED WITH Dopamine Agonist's?



IMPULSE CONTROL



AUGMENTATION

Impulse Control Disorder



11%



9%



5%



3%

17% of patients on Dopamine Agonist show impulse control issues

What is Augmentation?

- A worsening of RLS after an initial improvement with a dopamine medication
 - Levodopa (Sinemet)
 - Pramipexole (Mirapex)
 - Ropinirole (Requip)
 - Rotigotine (Neupro patch)

Signs of Augmentation NIH Criteria

- Worsening RLS symptoms after starting DA (Dopamine Agonist) therapy or tramadol (usually months to years)
- Earlier onset by at least 2 hours
- Increase in intensity of symptoms

Signs of Augmentation NIH Criteria

- Quicker onset of symptoms with rest
- Medication effect does not last as long
- Spread of symptoms to other body parts
- Periodic Limb Movements while Awake occur for the first time or are worse

How common is Augmentation?

- 60% of new Rx for RLS patients are DA
- 7-8% of patients per year develop augmentation
 - Irreversible and permanent worsening of RLS
 - Patients are miserable, often suicidal
- >75% of referrals to RLS experts
 - Pramipexole doses up to 12 mg
 - Ropinirole doses up to 24 mg

AASM Clinical Guidelines & FDA authorized Treatments

1. In adults with RLS, the AASM **recommends the use of gabapentin enacarbil** over no gabapentin enacarbil (strong recommendation, moderate certainty of evidence)

10. In adults with RLS, the AASM **suggests the use of bilateral high-frequency peroneal nerve stimulation** over no peroneal nerve stimulation (conditional recommendation, moderate certainty of evidence).

AASM Clinical Guidelines

FDA Non-Approved Treatments

2. In adults with RLS, the AASM **recommends the use of gabapentin** over no gabapentin (strong recommendation, moderate certainty of evidence).
3. In adults with RLS, the AASM **recommends the use of pregabalin** over no pregabalin (strong recommendation, moderate certainty of evidence).
- 4-7. In adults with RLS, the AASM recommends the use of **IV and oral iron therapy**
8. In adults with RLS, the AASM **suggests the use of dipyridamole** over no dipyridamole (conditional recommendation, low certainty of evidence).
9. In adults with RLS, the AASM **suggests the use of extended-release oxycodone and other opioids** over no opioids (conditional recommendation, moderate certainty of evidence).

$\alpha 2\delta$ drugs (Gabapentinoids)

Benefits

- Drug of first choice for RLS
- Best for painful RLS or RLS with painful neuropathy
- Helps with insomnia, anxiety
- No concerns about “addiction” or augmentation

Concerns

- Slower onset
- Long titration for gabapentin and pregabalin
- Daytime sleepiness/dizziness may occur
- Increase in depression/suicidal thoughts and behavior
- Weight gain/edema
- Dementia with long-term use?



Gabapentin

Initial dose (1-3 hours qhs or before Sx)

- 300 mg up to age 55
- 200 mg for ages 55-70
- 100 mg for ages > 70

Increase by initial dose q 3-7 days prn (max of 900-1200 mg/dose)

Add earlier (lower?) dose(s) up to tid prn

Reduce dose for renal impairment

Oral Iron Replacement Therapy

Serum ferritin < 50-75 (100) $\mu\text{g/L}$

- Ferrous Sulfate 325 mg qd, 1 hour AC with 100 mg Vitamin C

Oral iron therapy concerns

- GI problems (constipation, abdominal pain)
- Absorption
 - 20-30% with ferritin <5 $\mu\text{g/L}$
 - 2% with ferritin 60-80 $\mu\text{g/L}$

IV Iron Replacement Therapy

Slow-Release IV Iron formulations – 1000 mg

- Iron dextran (INFeD)
- Ferric carboxymaltose (Injectafer) **BLACK BOX WARNING**
- Ferumoxytol (Feraheme)

Do not use quick-release formulations

- Iron sucrose (Venofer)

Response

- Usually takes 1-2 months
- Do not check ferritin levels for 2-3 months
- Very well tolerated

OPIOID TREATMENT CONSENSUS GUIDELINES



CONSENSUS RECOMMENDATIONS

The Appropriate Use of Opioids in the Treatment of Refractory Restless Legs Syndrome



Michael H. Silber, MBChB; Philip M. Becker, MD; Mark J. Buchfuhrer, MD;
Christopher J. Earley, MBBCh, PhD; William G. Ondo, MD; Arthur S. Walters, MD;
and John W. Winkelman, MD, PhD; for the Scientific and Medical Advisory Board,
Restless Legs Syndrome Foundation

Low Dose Opioids for RLS

Name	Dose	Potency
codeine	15-60 mg every 4-6 hours	Low
meperidine	50-300 mg every 3-4 hours	Low
hydrocodone	2.5-10 mg every 4-6 hours	Medium
tramadol	50-100 mg every 6 hours	Medium
oxycodone	2.5-10 mg every 6 hours	High
Oxycodone Long-Acting	10-20 mg every 8-12 hours	High
methadone	5-10 mg every 8 hours	High
levorphanol	2-4 mg every 6-8 hours	High
hydromorphone	2-8 mg every 4-6 hours	High
Morphine CR	15-30 mg every 8-12 hours	High
Oxymorphone	2.5-10 mg every 6 hours	High
Oxymorphone ER	5-10 mg every 12 hours	High
Tapentadol	50-100 mg every 4-6 hours	High
Tapentadol ER	50-200 mg every 12 hours	High

Low dose opioids for RLS

- Acetaminophen, ASA, Ibuprofen
 - Do not help RLS
 - Therefore, avoid combination medications such as acetaminophen-hydrocodone or acetaminophen-oxycodone
 - Use “pure” opioids like methadone, oxycodone, morphine, etc.
- Methadone
 - Very commonly used
- Oxycodone
 - Immediate or slow-release

Buprenorphine for RLS

- Buprenorphine –partial agonist at opioid mu receptor
 - Buccal Film (Belbuca - buprenorphine)
 - Rx for pain - expensive
 - 75 mcg initial dose, avg. 150-450 mcg
 - Sublingual film (Suboxone - buprenorphine/naloxone)
 - Rx for opioid dependence
 - 2 mg film, cut into 1/8-1/4 initial dose, avg. 1/4 (500 mcg)-1 film
 - Sublingual pill (Subutex - buprenorphine)
 - Rx for opioid dependence
 - 2 mg tablet, initial dose – 1/2 tablet
 - Transdermal patch (Butrans - buprenorphine)
 - Rx to treat pain
 - 7.5, 10, 15, and 20 mcg/hour, weekly patch
 - When oral formulation not tolerated – 480 mcg/day max dose

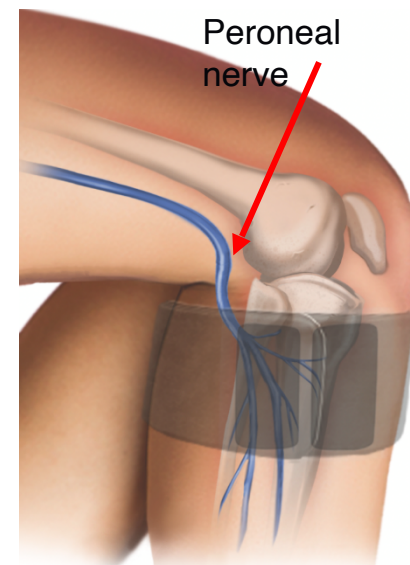
Buprenorphine for RLS

- May help depression
- Less risk of resp. depression - “ceiling effect”
- High affinity for the mu opioid receptor
- No MEDD equivalence
- Schedule III – can give refills
- Dental issues –cavities, infection, tooth erosion/loss

The **TO**nic **MO**tor **AC**tivation (TOMAC) solution

Terminology (it can get confusing...)

- *Scientific term for the technology:* **Tonic motor activation (TOMAC) = High-frequency peroneal nerve stimulation**
- **NPNS = Noninvasive Peroneal Nerve Stimulation**
- *Medical device:* **Nidra** is the brand name for the only medical device that delivers TOMAC (nidrarls.com)
- Bilateral external high frequency electrical stimulation of low-threshold muscle afferents in the peroneal nerve¹
 - Tonic: Nidra increases muscle tone in an isometric manner that doesn't cause leg twitches → ***sleep-compatible***
 - High-frequency (4000Hz): Bypasses pain fibers in the skin to activate the peroneal nerve below → ***sleep-compatible***
 - Long-lasting: 30min continuous tonic activation → ***hours of symptom suppression***
 - 67% for at least 2 hours after session
 - 86% for at least 30 minutes after session



¹Charlesworth et al. JCSM. July 2023; 19(7)

²Bogan et al. Sleep. July 2023; 46(10)

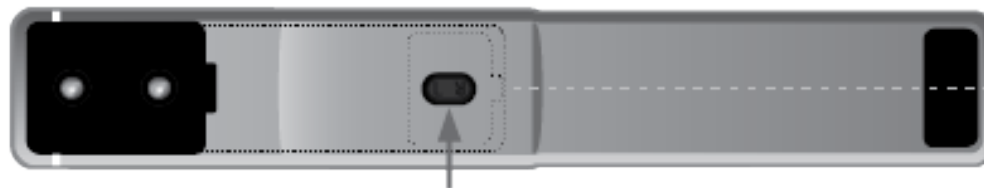
NTX150

Control Buttons

Light bar and controls in vertical orientation for enhanced user experience.

Treatment Levels

Status Indicator

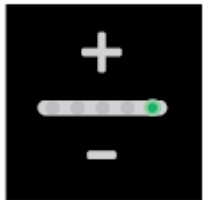


L/R Identification LED

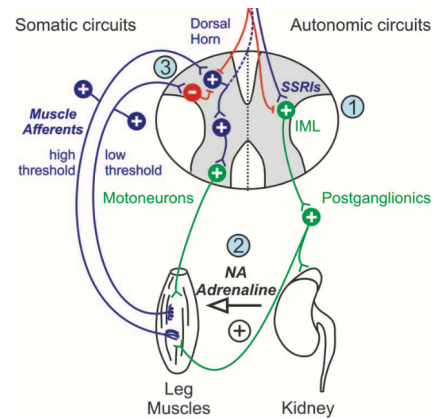
USB-C



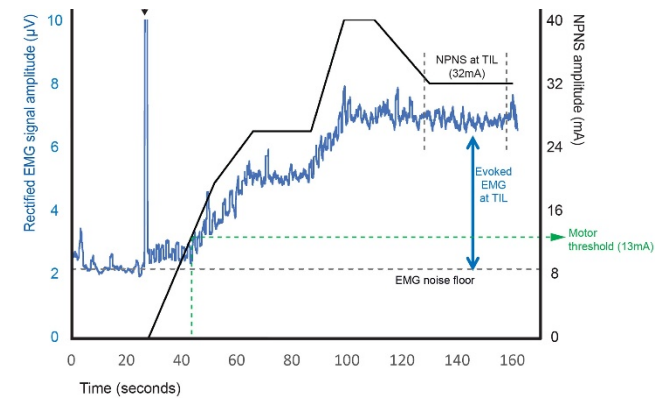
NTX100



Mechanism of Action



Clemens et al. Neurology. July 2006; 67(1).



Charlesworth et al. JCSM. July 2023; 19(7).

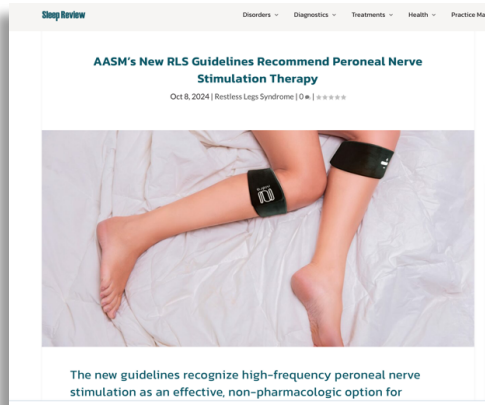
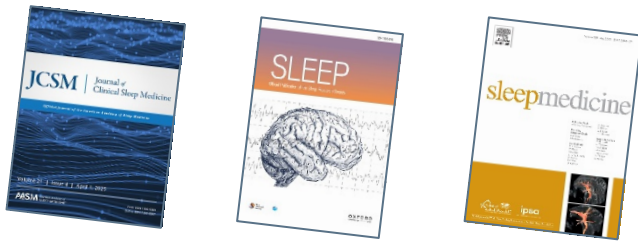
1 Bilateral high frequency stimulation of the peroneal nerve below the neck of the fibula

2 Evokes afferent, reflexive activation of the tibialis anterior muscle¹

3 This afferent mechanism provides critical benefits
Isometric (non-jerky) / Long-lasting (non-fatiguing) / Sleep compatible

Clinically proven efficacy and safety

5 clinical trials and 10 peer-reviewed publications



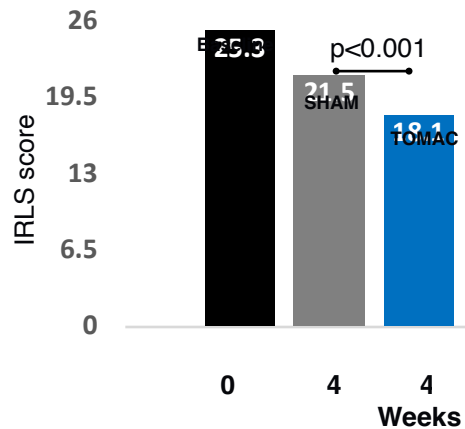
- ① **Very Effective:** *long-lasting clinically significant improvements in both RLS (IRLS, CGI-I) and sleep quality (MOS)^{1,2}*
- ② **Low-risk:** *No systemic, severe, or serious side-effects¹*
- ③ **FDA approved for refractory RLS (2023)**
- ④ **Recommended in 2025 AASM Clinical Practice Guidelines³**
- ⑤ **Covered by Medicare**

1. Bogan RK, et al. Sleep. July 2023;46(10). 2. Roy A, et al. Sleep. 2023;46(10). 3. Winkelman JW, et al. JCSM. Jan 2025;21(1)

Pivotal trial – Phase 2 outcomes

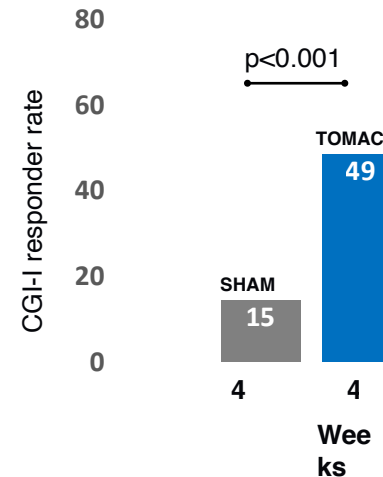
IRLS Score

Patient-rated RLS improvement



CGI-I Responder Rate

Clinician-rated RLS improvement

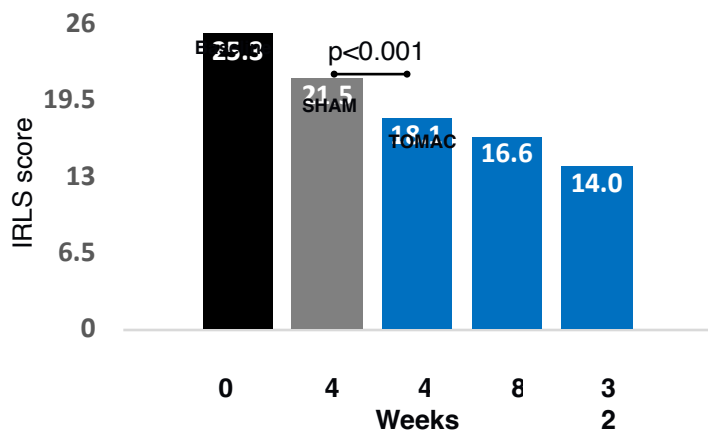


**Statistically significant
improvements with TOMAC
compared to sham**

Pivotal trial – Phase 2 outcomes

IRLS Score

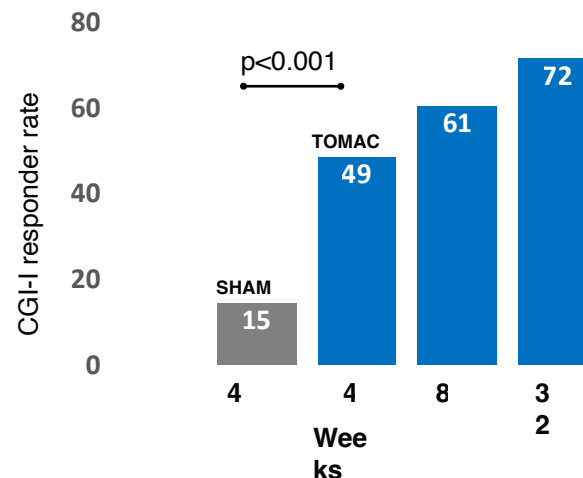
Patient-rated RLS improvement



↓ **11.3 pt** reduction
in IRLS score at 32-weeks

CGI-I Responder Rate

Clinician-rated RLS improvement



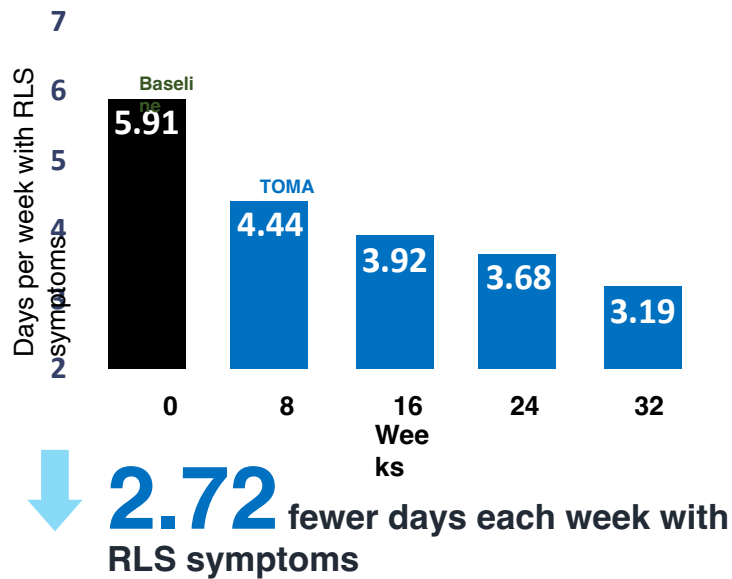
73% of patients showed clinically
significant improvement at 32 weeks
(>85% had any improvement)

**Greater improvement with continued
use**

Pivotal trial – Phase 2 outcomes

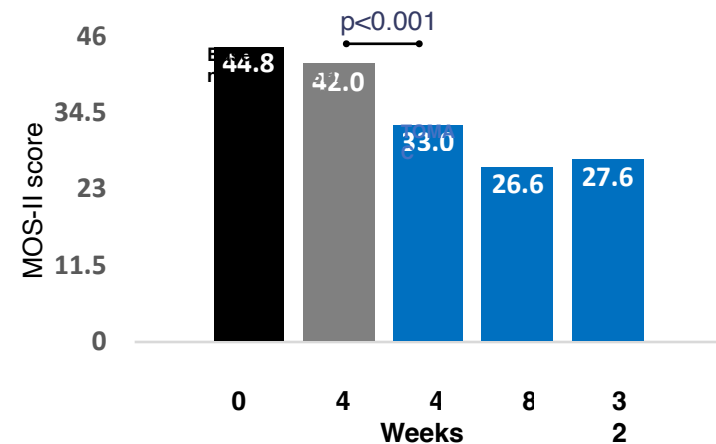
Days/week with RLS symptoms

Symptom frequency



MOS-II Sleep Problems Index

Patient-rated sleep improvement



↓ **38%** reduction in sleep problems index at 32 weeks

- Fell asleep faster
- Better daytime functioning

Improvement in sleep and frequency of RLS

RESTFUL study: the pivotal trial

82%

acute relief **starts**
within 30 minutes¹

67%

relief from a single
session **lasts >2-hours**
for 67% of responders²

91%

improved RLS at 8-
weeks based on CGI-
I<4 points³

2.7x

increase in symptom-
free days

0

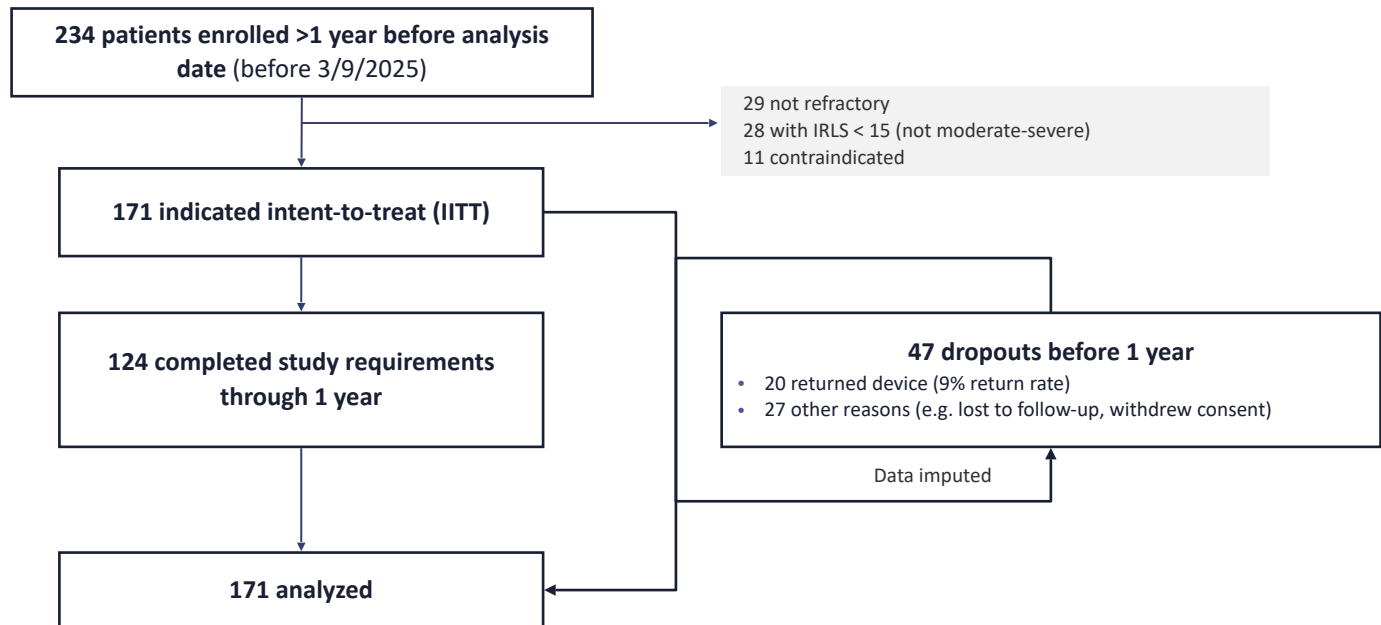
serious device-related
adverse events^{2,3}

1. Noctrix Health. Data on File. CL-10 Report. 2. Bogan RK, et al. Sleep. 2023;46(10). 3. Roy A, et al. Sleep. 2023;46(10).

THRIVE study

Interim 1-year indicated intent-to-treat analysis (Thrive Study)

- Adults with refractory, moderate to severe RLS
- Observational “real world” study



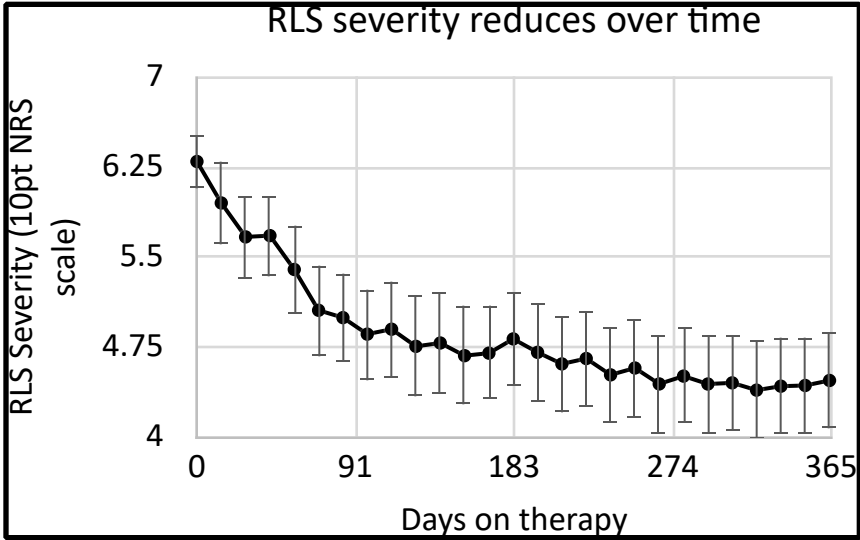
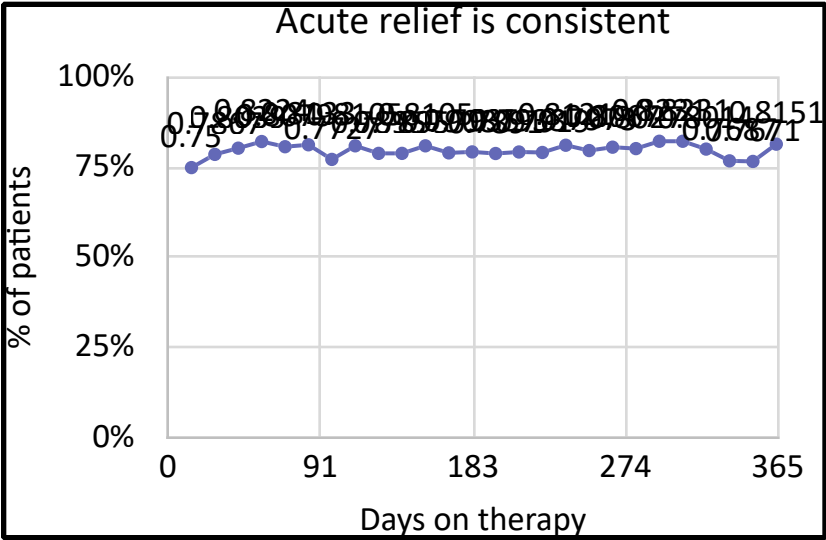
Long-term safety and tolerability

- 0 serious or severe device-related adverse effects
- 2 tolerability-related discontinuations (1 muscle spasm, 1 discomfort)
- Administration-site skin reactions are the most common side-effect (9% mild, 4% moderate)

Summary of device-related AEs	
	% of patients
Any device-related AE	19%
Severe	0%
Serious	0%
Led to discontinuation	1%
MedDRA Categorization	
Administration site reaction	13%
Discomfort	6%
Restless Legs Syndrome	2%
Muscle spasm	1%
Plantar fasciitis	1%

Multiple timescales of relief

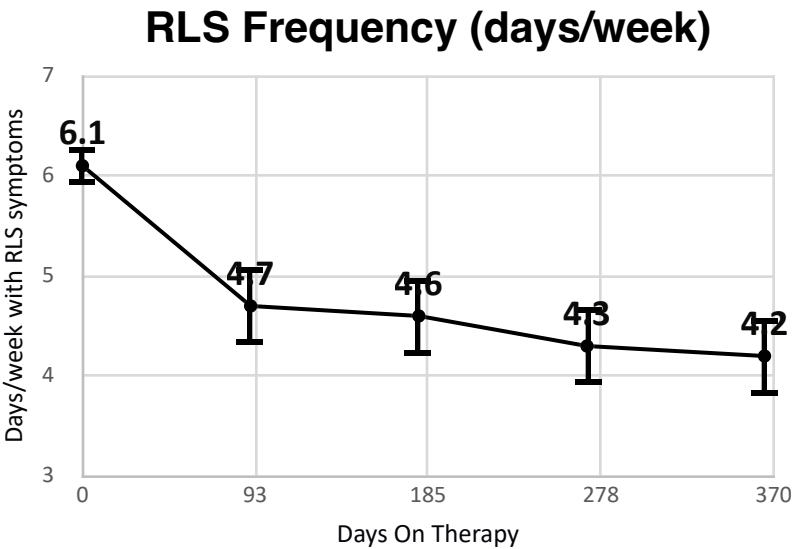
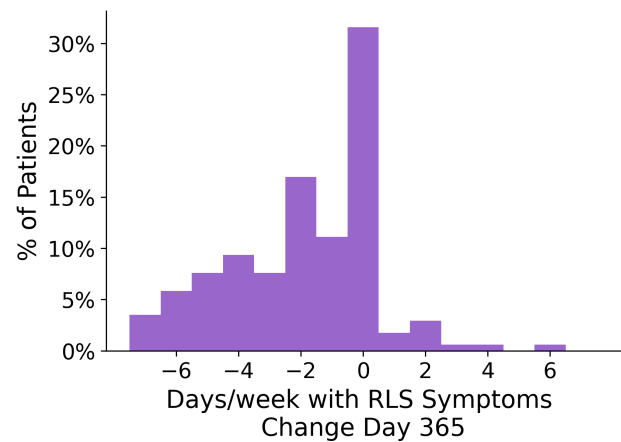
- **Acute relief** starts in the first few weeks and is consistent
- **RLS severity** reduces more gradually over time



Reduction in frequency of RLS symptoms

- Reduction in days per week of RLS symptoms

Change from baseline to 1-year (n=171)	
RLS Frequency (days/week)	-1.9



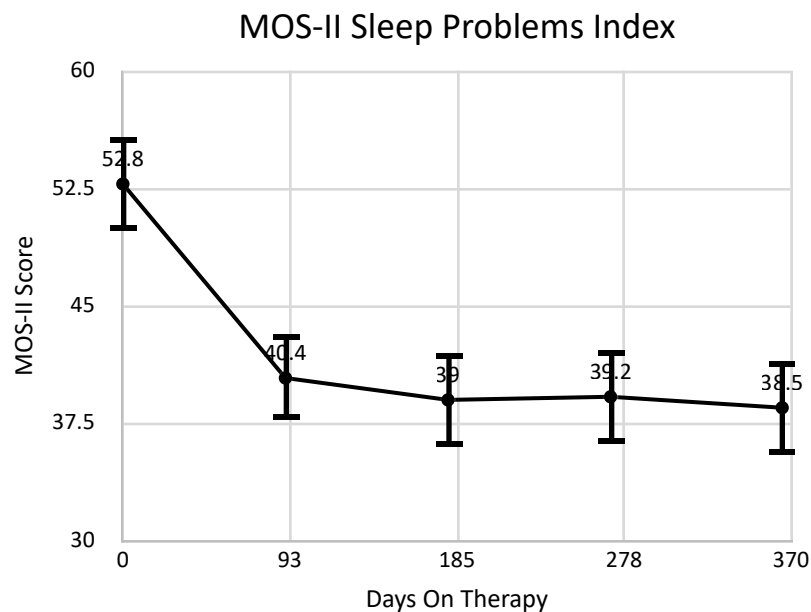
Improvement in sleep

- **Subjective sleep improvement** on MOS-II is similar to RESTFUL clinical trial results
- Reduction in likelihood of moderate-severe **daytime sleepiness** (ESS ≥ 13) from 26% to 13%
- Significant improvement in daytime somnolence, sleep disturbance, and sleep adequacy

Change from baseline to 1-year (n=171)

MOS-II change

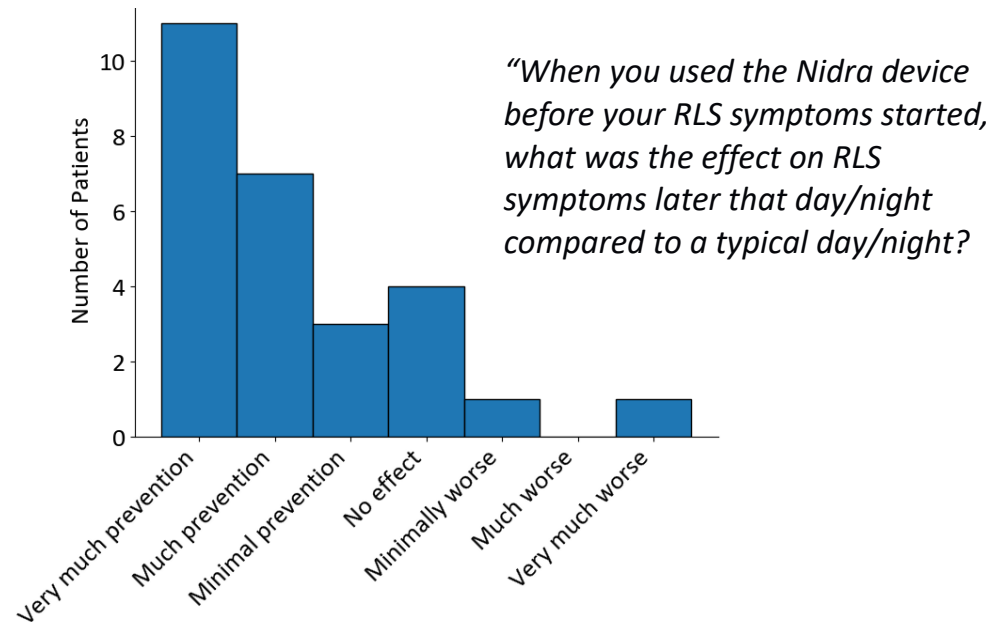
-14.3



- Improvements in time to fall asleep, ability to stay asleep, and daytime sleepiness

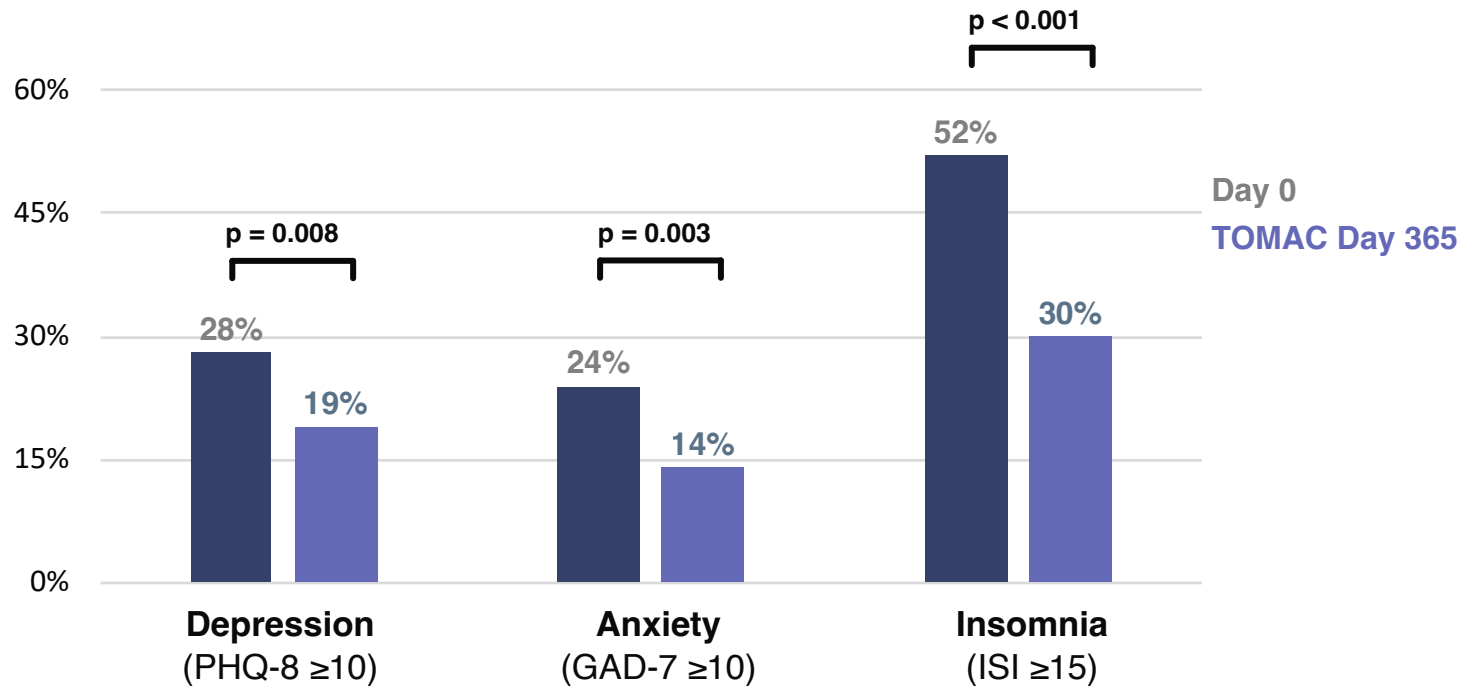
Prophylactic Use of TOMAC

- Exploratory question asked patients if they used it when not experiencing symptoms
- 29 patients (out of 71 who responded) used without symptoms (41%)
- Only 2 reported worsening of symptoms



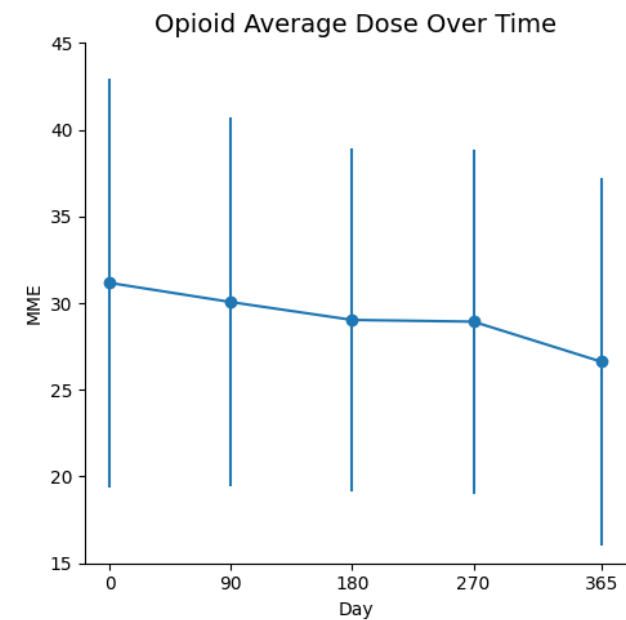
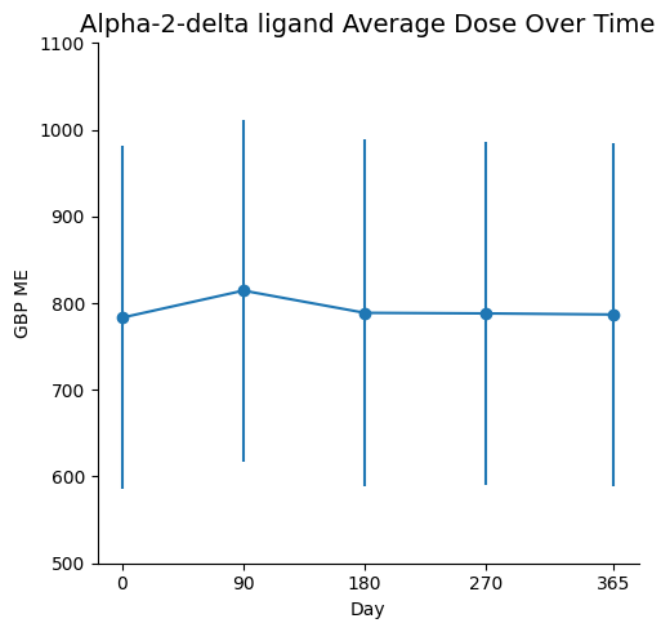
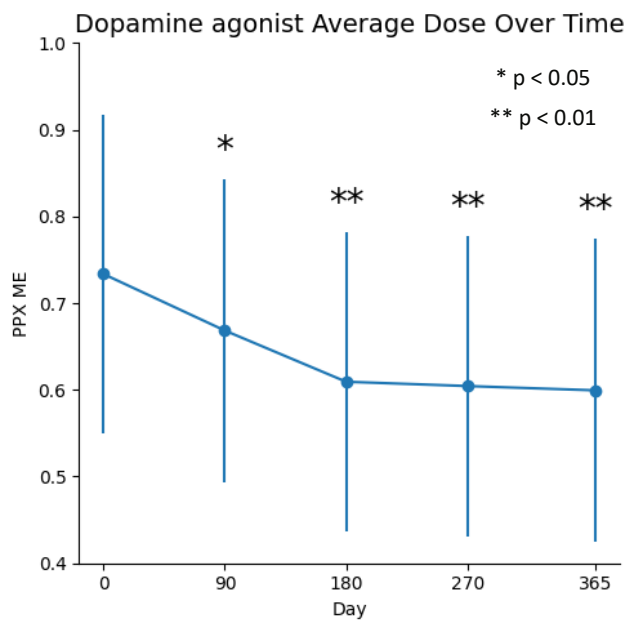
Impact on comorbidities

- Largest improvement was in ISI question: “How *WORRIED/DISTRESSED* are you about your current sleep problem?”



RLS medication dosage over time

- Average of only patients who were on each medication AND did not change dosage of other medications
- Dopamine agonist dose is significantly reduced after day 180, 270, and 365 compared to baseline
- Alpha-2-delta ligand and opioid dose not significantly different at later visits compared to baseline



Who is a responder to TOMAC?

Adherence is the main predictor

- **Effectiveness requires 3 factors (PIT)**
 - *Positioning* – on the peroneal nerve
 - *Intensity* – activate peroneal nerve & generate TOMAC
 - *Timing* – frequent enough to result in meaningful improvement
- **Therapy support on these 3 factors is essential (PIT)**
- **Other factors**: patient at max allowed intensity (40mA) and needs more



Important Safety Information

Contraindications

The Nidra TOMAC System is contraindicated for use in patients with the following:

- Diagnosis of epilepsy or other seizure disorder
- Active medical device implant anywhere in the body, including but not limited to pacemakers, spinal cord stimulators, deep brain stimulators
- Metal implant in the leg at the therapy site (not including knee replacements)
- Known allergy to device materials (or severe previous reaction to medical adhesives or bandages)
- Cellulitis, open sores, or injury at or near the location of therapy device application
- The device cannot be used while driving, operating machinery, or during any activity in which electrical stimulation can put the patient at risk of injury

Potential Complications There is a potential for the following side effects, which are typically mild to moderate and resolve over time:Mild skin irritation from use of adhesives.

- Temporary interference with sleep while wearing the device. For some people, the device may be uncomfortable. For others, the device may interfere with preferred sleep positions.
- Proper use of the device as described in the Instructions for Use (IFU) can help reduce or prevent the following complications: Discomfort, paresthesia (tingling or prickling sensation), or otherwise irritating or uncomfortable sensations during treatment. This risk is reduced by adjusting the stimulation intensity.

This list is not all inclusive. Please refer to the [Instructions for Use](#) for all of the important warnings and precautions before using or prescribing this product.

Summary of New RLS Treatment Guidelines

Do not prescribe dopamine drugs!

Start with gabapentinoids

TOMAC neurostimulation bands

IV iron

- 1000 mg of INFeD, Injectafer or Feraheme

Low Dose Opioids

